On page 8, lines 16-21, the specification explains that the present invention allows the immobilization of both unmodified and **modified biopolymers** on substrates by simple air-drying on the substrate. The term "modified biopolymer" is defined as a biopolymer with introduced functional groups. An example of a modified polymer, such as biotinylated biopolymer, is also provided. Additional examples of modified biopolymers, such as thiol- or amino-modified DNA, is provided on page 5, lines 25-30. Based on this description, those skilled in the art would have understood that, at the time the application was filed, the inventors had the possession of the modified probe and target biopolymers and methods of their attachment to substrates to form a probe assay article or a target assay article. Accordingly, the modified biopolymers were adequately described in the instant specification and do not constitute new matter. Therefore, applicants submit that the rejections of claim 56 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claim 56 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it uses the term "modified." This rejection is respectfully traversed.

The term "modified" is clear in view of its English language meaning and in further view of the instant specification. The Random House Webster's Unabridged Dictionary of the English Language (Second Edition, 1997) defines the meaning of the verb "modify" as "to change somewhat the form or qualities of" (page 1236). Accordingly, the English language meaning of the term "modified" is "changed in form or quality."

The English language definition of the term "modified" is further clarified in the specification. As discussed above, the term "modified biopolymer" is specifically defined in the specification as a biopolymer with introduced functional groups. Additionally, the specification provides examples of modified polymers, such as biotinylated biopolymers, and thiol- and amino-modified DNA. Finally, the specification states on page 8, lines 16-18, "[u]nlike the related art, which uses chemical crosslinking of biopolymers to the substrates, the present invention allows

immobilization of both unmodified and modified biopolymers on substrates by simple air-drying on the substrate." Therefore, applicants submit that not only is that term "unmodified" definite and fully compliant with 35 U.S.C. § 112, but that it recites an important aspect of the present invention not described or suggested in the prior art of record.

Claims 64-68 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,970,144 (the '144 patent). This rejection is moot with respect to claim 67 due to the cancellation of the claim. With respect to claims 64-66 and 68, this rejection is respectfully traversed.

The Examiner appears to disregard the qualifying term "modified" in the phrase "modified substrate" because the Examiner finds the term "modified" unclear. Applicants disagree. On page 7, lines 6-10, the specification states:

> The direct adsorption is further improved by modifying the substrates prior to contacting them with biopolymers. The **substrates may be modified by introducing a functionality selected from a group consisting of: amino, carboxyl, thiol, and their derivatives**. In one embodiment, the substrate is modified by introduction of an amine group.

Also, the specification describes specific methods, such as plasma discharge, that may be used to modify the substrates (page 7, lines 11-22). Therefore, in accordance with the specification, the term "modified substrate" means a substrate having a surface that has been altered to contain certain functional groups.

Furthermore, claim 64, as amended, emphasizes that in the present invention, polypeptides are directly adsorbed on the substrate by contacting a polypeptide with a surface of the substrate and drying the substrate. It is an unexpected discovery of the present invention that modified substrates, such as plasma-aminated polypropylene and polysterene substrates, are capable of direct and stable adsorption of polypeptides without the need for additional fixing steps, such as those commonly used in enzyme-linked immunosorbent assays (ELISA) (page 8, lines 13-21). Consequently, the present invention provides a number of advantages over the conventional methods. The advantages include, for example, a

simplification of the production of polypeptide arrays and a decrease in their manufacturing costs (page 5, lines 25-30).

The '144 patent does not anticipate instant claim 64 because it does not teach providing a **modified** substrate as defined in the present specification and explained above. Additionally, the '144 patent does not anticipate the instant claim 64 because it does not teach "contacting either the probe or target polypeptide with a surface of the substrate and drying the substrate whereby either the probe or target polypeptide **directly adsorbs and immobilizes** on the substrate surface."

Instead, the '144 patent teaches using conventional microtiter dishes for "typical ELISA assay" (column 11, lines 34-43). Such conventional microtiter plates do not have modified surfaces as defined in the present invention. Furthermore, in a "typical ELISA assay," a protein is not immobilized by drying as in the present invention, but rather chemically fixed onto the dish (see step 3 of the ELISA procedure in columns 13-14 of the '144 patent).

The '144 patent does not suggest instant claim 64, because it does not suggest the immobilization of polypeptides by drying. At most, the '144 patent teaches a conventional ELISA assay with a two-step immobilization of protein. The first step involves an overnight drying of 50µl of the protein solution in the wells of a conventional microplate and the second step involves the immobilization of protein by "filling the wells with absolute methanol **to fix the protein** onto the dish" (column 14, lines 1-2). Based on such teaching, those skilled in the art would have not been motivated to modify the material of standard microplates to arrive at the modified substrates of the present invention, much less to omit the protein-fixing step of the standard ELISA protocol without the hindsight of the present invention. Therefore, the '144 reference does not teach or suggest the immobilization of polypeptides by drying on modified substrates and, thus, does not anticipate or make present claim 64 obvious. Claims 65-66 and 68 depend on claim 64, directly or indirectly, and are patentable over the '144 patent for at least the same reasons.

Claims 29-42 and 55-63 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Head et al., U.S. Patent No. 6,322,968 (the '968 patent), in view of Groet et al., U.S. Patent No. 4,588,682 (the '682 patent). This rejection is respectfully traversed.

As it has been explained in the reply to the previous Office Action, independent claim 29 requires direct adsorption of biopolymers on the substrate by contacting a biopolymer with a surface of the substrate and drying the substrate. It is an unexpected discovery of the present invention that modified substrates, such as plasma-aminated polypropylene and polysterene substrates, are capable of direct and stable adsorption of biomolecules without any chemical spacer arms or links by drying biopolymer solutions on the substrates (page 8, lines 13-21). Of course, a biomolecule directly adsorbed on the surface itself may serve as a linker for the attachment of another biomolecule.

The Examiner acknowledged that the '968 patent does not disclose direct adsorption of the probe or target biopolymer on the substrate surface, but relies on the '682 patent for such teaching. Applicants respectfully disagree with the Examiner's reading of the '682 patent.

The '682 patent states that its invention is directed to a method of binding nucleic acid to a support by depositing the nucleic acid on the support and then contacting the nucleic acid and the support with a liquid-binding solution which contains an **organic solvent capable of binding** the nucleic acid to the support (column 1, lines 25-32). Additionally, the '682 patent emphasizes the importance of selecting an organic solvent that "will bind nucleic acid" (column 2, lines 1-2). Finally, the '682 patent provides an example of binding DNA to a membrane by "immersing the membrane in anhydrous sec-butyl alcohol for 5 min." (column 2, lines 51-54). Therefore, the method described in the '682 patent does not disclose that the probe or target biopolymer is directly adsorbed on the substrate surface as stated by the Examiner, but instead it teaches the immobilization of nucleic acids by chemical adhesion and covalent bonding.

Also, the Examiner appears to believe that the '682 patent anticipates instant claim 29 because in the Background of the Invention section, the text states:

> This invention relates to binding nucleic acids (RNA and DNA) to supports, e.g. to carry out DNA hybridization assays.
>
> Such assays have been used to detect specific DNA sequences in samples for several years, and are described in the patent and technical literature, e.g. Falkow et al. U.S. Pat. No. 4,358,535, hereby incorporated by reference. Such assays typically involve **spotting a sample**, e.g. urine, suspected of **containing a particular DNA sequence (in viruses or prokaryotic or eukaryotic cells in the sample)** onto a DNA-binding support, e.g. a nitrocellulose membrane, lysing the cells, if necessary, denaturing and neutralizing the DNA, and then affixing the DNA to the support prior to carrying out the hybridization assay. Affixation is typically carried out **by air drying followed by drying in a vacuum oven** for two hours, as described, e.g., in Gillespie et al. (1965) J. Mol. Biol. 12, 829.

Again, applicants disagree with the Examiner's reading of the '682 patent. The '682 patent does not teach that DNA may be affixed to a substrate by contacting DNA with the substrate and drying the substrate whereby DNA directly adsorbs on the substrate as required by step (c) of instant claim 29. Instead, the '682 patent teaches **spotting cells** containing DNA onto a support, liberating DNA by lysing the cells, and affixing the released DNA by denaturing and neutralizing DNA, and finally by baking DNA onto the support. There is nothing in the above-cited statement that would indicate to those skilled in the art that air-drying of DNA alone without baking in the oven would result in DNA immobilization, much less that DNA may be affixed to a substrate by contacting DNA (instead of the cells) with a substrate and air-drying the substrate.

Additionally, U.S. Patent No. 4,358,535 (the '535 patent), cited by the '682 patent, further elaborates on the DNA hybridization assay (column 4, lines 26-68):

> For unicellular organisms, a particularly useful technique is colony hybridization... The **clinical isolate or specimen is spotted** or spread onto a filter to provide a plurality of individual portions. The filter is an inert porous solid support, e.g. nitrocellulose. The clinical isolate may be any excreta or physiological fluid, such as stool, urine, sputum, pus, serum, plasma, ocular lens fluid, spinal fluid, lymph, genital washings, or the like...
>
> The **cells are then treated t liberate their DNA** (and/or RNA)... Lysis conditions are devised such that the cells or colonies do not migrate and

> their DNA remains affixed in place on the surface where they were situated. The **lysing and DNA denaturing** as well as the subsequent washings can be achieved by placing the filter containing the cells or colonies, isolate side up, onto a bibulous support saturated with an appropriate solution for a sufficient time to lyse the cells and denature the DNA. For lysing, chemical lysing will conveniently be employed, usually dilute aqueous alkali e.g. 0.1 to 1 M NaOH. The alkali will also serve to denature the DNA. Other denaturation agents include, elevated temperatures, organic reagents, e.g. alcohols, amides, amines, ureas, phenols and sulfoxides or certain inorganic ions, e.g. thiocyanate and perchlorate.
>
> ...
>
> After the lysing, denaturing and washes have been accomplished, the DNA spotted filter is dried at an elevated temperature, generally from about 50.degree. to 70.degree. C. The DNA is now fixed in position and can be assayed with the probe when convenient.

Clearly, the DNA hybridization method noted in the Background Section of the '682 patent requires contacting whole cells (not DNA) with a support, lysing the cells to release DNA, denaturing and neutralizing DNA, and then immobilizing the denatured and neutralized DNA by baking it onto the support at 50°C-70°C. Thus, the '682 patent does not teach that DNA may be affixed to a substrate by contacting DNA directly with the substrate and drying the substrate whereby DNA adsorbs on the substrate as required by step (c) of instant claim 29.

Additionally, teachings of the Background Section of the '682 patent cannot be combined with the teachings of the '968 patent as suggested by the Examiner. As discussed above, the '682 patent requires denaturation of DNA prior to immobilization and baking DNA at 50°C-70°C in order to immobilize the DNA. On the other hand, the '968 patent utilizes pre-synthesized nucleic acid molecules that are not denatured and are affixed to a substrate at room temperatures (see Example 3 in column 18).

Therefore, claim 29 is neither anticipated nor rendered obvious by the '682 and '968 patents, either alone or in combination. Claims 30-42 and 55-63 depend, directly or indirectly, from patentable claim 29 and are, therefore, believed to be patentable for at least the same reasons as claim 29.

Claim 69-70 are rejected under 35 U.S.C § 103(a) as being unpatentable over the '144 patent. This rejection is respectfully traversed.

As explained above, independent claim 64 is patentable over the '144 patent. Claims 69-70 depend, directly or indirectly, from patentable claim 64 and is, therefore, believed to be patentable for at least the same reasons as claim 64.

Applicant believes the foregoing amendments comply with the requirements of form and thus may be admitted under 37 C.F.R. § 1.116(a). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(b). In this connection, these amendments were not earlier presented because they are in response to the matters pointed out for the first time in the Final Office Action.

Lastly, admission is requested under 37 C.F.R. § 1.116(a) as presenting the rejected claims in better from for consideration on appeal.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,

HOGAN & HARTSON L.L.P.

Date: September 18, 2002

By: _____

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Version with markings to show changes made:

Please replace the text of claims 64 and 68-70 with the following text:

64. (Amended) A method of detecting a polypeptide contained in a sample, comprising the steps of:

(a) providing a modified substrate;

(b) providing a probe polypeptide that can form a complex with the target polypeptide;

(c) contacting either the probe or target polypeptide with a surface of the substrate [under a condition sufficient for a direct adsorption of] and drying the substrate whereby either the probe or target polypeptide directly adsorbs and immobilizes on the substrate surface to form a probe assay article or a target assay article, respectively;

(d) contacting the probe assay article with the target polypeptide, or contacting the target assay article with the probe polypeptide under a condition that allows the formation of a complex comprising the probe and the target polypeptides; and

(e) detecting and determining the presence of the complex as a measurement for the presence or the amount of the target polypeptide contained in the sample.

68. (Amended) The method of claim [67] 64, wherein the amount of the probe polypeptide or the target polypeptide contacted with the substrate in step (c) ranges from about 10^{-20} to about 10^{-14} moles.

69. (Amended) The method of claim [67] 64, wherein the aliquot is from about 0.1 nL to about 500 nL.

70. (Amended) The method of claim [67] 64, wherein the drying is air-drying conducted for a period ranging from about 5 minutes to about 60 minutes.